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TITLE: Intervention Study of Flaxseed in Postmenopausal Women:
Effects on Hormonal Biomarkers of Breast Cancer Risk

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Introduction: It has been hypothesized that plant-derived estrogens (phytoestrogens) play an important role in the etiology of breast cancer. One class of phytoestrogens known as lignans are present in a variety of fruits, vegetables, and grains, but flaxseed is by far, the richest source. Laboratory and cross-sectional studies indicate that lignans are favorably associated with important hormonal biomarkers of breast cancer risk, including elevated serum levels of sex-hormone binding globulin and lower serum levels of estradiol and testosterone. The objective of this study is to determine if flaxseed supplementation to usual diet in postmenopausal women has a beneficial effect on important hormonal biomarkers of breast cancer risk. The specific aims of this study are to determine if (1) flaxseed intake lowers serum levels of estradiol and testosterone and increases serum levels of sex-hormone binding globulin; (2) flaxseed intake increases the urinary excretion ratio of 2/4-OHE1 and 2/16a-OHE1 and decreases the urinary excretion ratio of genotoxic estrogen metabolites to total estrogens (16a-OHE1 + 4-OHE2 + 4OHE1)/total estrogens; and (3) higher doses and longer duration of flaxseed intake results in greater changes to the aforementioned variables. Participants in this study will be volunteers recruited from the University of Massachusetts area. The pre-post intervention study will involve a total of 50 postmenopausal women. Participants will receive 6 weeks of usual diet plus 12 grams per day of raw flaxseed, followed by 6 weeks of usual diet plus 24 grams per day of raw flaxseed. Serum and urinary levels of hormonal biomarkers of breast cancer risk will be assessed at baseline, 7 weeks, and 13 weeks. The project will establish whether flaxseed may be a useful dietary strategy in the prevention of breast cancer. After discussion with the COR, no further justification regarding the dosing schedule is necessary because this information is detailed in the protocol.

Body:

Tasks 1-4: Study participant recruitment and collection of biological specimens is complete. A total of 47 eligible study subjects successfully completed the study.

Task 5: Laboratory analyses of serum hormone levels were completed by the University of Southern California Reproductive Endocrine Laboratory. Duplicate quality control specimens from two postmenopausal women were inserted into each of the four batches. Between batch coefficients of variations ranged from 8.1% to 9.4% for testosterone, 11.5% to 12.9% for estrone, 14.3% to 15.5% for estradiol; and 3.9% to 6.4% for SHBG, indicating that laboratory assays were of acceptable quality. Urine specimens have been sent to Dr. Mindy Kurzer (University of Minnesota), and laboratory analyses of estrogen metabolites and lignans are underway. Results are expected by September 2004.

Task 6-7: Table 1 describes the preliminary findings of the association between dietary flaxseed and changes in serum hormone levels. Serum levels of estrone, estradiol and testosterone appeared to decline after flaxseed supplementation although these changes were not statistically significant and there was no evidence that levels declined more at increasing levels of dose and duration of intake. Serum levels of SHBG were unchanged.

Adjustment for changes in other factors, including weight, physical activity and dietary factors had little impact on these findings. Statistical analyses of the association between dietary flaxseed and changes in urinary hormone data is expected to begin in September 2004.

<i>Table 1. Change in hormone outcomes between each intervention visit</i>	Change from Baseline to Follow-up 1 ^{ac}	Change from Baseline to Follow-up 2 ^{bd}
Testosterone (pg/ml)	-9.91 ± 6.92	-4.65 ± 6.54
95% CI	(-23.83, 4.01)	(-17.81, 8.52)
p-value	0.16	0.48
Estrone (pg/ml)	-2.60 ± 2.06	-3.26 ± 2.23
95% CI	(-6.74, 1.54)	(-7.75, 1.22)
p-value	0.21	0.15
Estradiol (pg/ml)	-2.71 ± 1.93	-4.36 ± 4.10
95% CI	(-6.59, 1.17)	(-12.80, 3.89)
p-value	0.17	0.29
SHBG (nmol/ml)	0.59 ± 1.54	0.04 ± 1.79
95% CI	(-2.51, 3.67)	(-3.57, 3.64)
p-value	0.71	0.98

^an = 48; ^bn = 47; ^c(Follow-up 1 – Baseline); ^d(Follow-up 2 – Baseline);
^e(Follow-up 2 – Follow-up 1)

One study participant notified the Principal Investigator that she was experiencing a vaginal discharge that began during the study that had continued to worsen during the four months after stopping flaxseed. She was concerned that this adverse health event could be related to flaxseed intake. As part of her own routine primary care, she had been worked up for bacterial, fungal and yeast infections and had a PAP smear and pelvic ultrasound which were within normal limit. After notifying the institutional IRB about this reported occurrence and reviewing the published literature, she was informed by the Principal Investigator that there is no available evidence to suggest that this event would be related to the ingestion of flaxseed.

Key Research Accomplishments

- Preliminary findings indicate that serum levels of estrone, estradiol and testosterone declined after flaxseed supplementation but these findings were not statistically significant, and there was no evidence of greater declines with increasing dose and duration of intake.
- Urinary specimens have been sent to Dr. Mindy Kurzer, and are currently being analyzed for lignan level (as a measure of compliance) and estrogen metabolites.

Conclusions:

Our preliminary findings suggest that dietary flaxseed may have modest beneficial effects on serum hormone levels that are important in the etiology of breast cancer. Additional studies focusing on the direct effects on flaxseed on breast tissue appear warranted. Additional larger studies with a control group would also be desirable.

Contractual Issues

After discussion with the COR, no additional justification of the 36-month performance period is necessary.

Reportable Outcomes:

An application submitted to the American Institute of Cancer Research was funded to examine the effects of dietary flaxseed on other blood biomarkers of cancer risk (i.e., insulin-like growth factor, insulin-like growth factor binding protein, c-peptide) using remaining blood specimens from this study. The title of this proposal is "Intervention Study of Flaxseed in Postmenopausal Women: Effects on Biomarkers of Cancer Risk". After discussion with the COR, the grant number is not necessary as this is not a DOD grant.

References: Not Applicable

Appendices: Not Applicable.